

## PATTERN OF DRUG RESISTANCE IN PULMONARY TB PATIENT IN NWFP

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### ABSTRACT

**Background:** The emergence of tuberculous bacillus species resistant to various anti tuberculous drugs has become a serious global threat to the human health. Drug resistance is either primary (from a host harboring resistant tubercle bacilli) or acquired (develops during treatment with anti tuberculosis chemotherapeutic agents because of poor patients compliance or inadequate/inappropriate treatment regimens). This study is done to evaluate the pattern of drug resistance in our population.

**Materials and Methods:** The record of the patients who attended the chest clinic at Peshawar from 1993-2003 due to suspected drug resistant tuberculosis was analyzed. Those who had a sputum culture and sensitivity report indicating resistance to at least two anti-TB drugs (Rifampicin & INH) were included in the study. Data, including demographic data, sputum smear, and sputum culture were recorded in a specified Performa.

**Results:** Drug resistance was suspected in 77 patients. 43 (56%) were males and 34 (44%) were females, with the age range of 15-60 years (mean age 32.5 years). 4 patients excluded after their sputum C/S showed no growth after 6 weeks of inoculation period. 73 patients were left for further analysis.

Culture and sensitivity report showed the following results. 26 patients (36 %) were resistant to all six drugs i.e Isoniazid (INH), Rifampicin ( R ), Streptomycin (S), Ethambutal (E), Pyrazinamide (Z) and Thiocetazone (TH). 15 (20%) had resistance to five drugs. 16 patients (22%) were resistant to four drugs while 10 patients (14%) had resistance to three drugs. Only 6 patients (8%) were resistant to combination of Rifampicin and INH i.e 2 drugs. The resistance contributed by individual drugs was: Streptomycin: 66.6%, Rifampicin: 100%, INH: 100%, Ethambutal: 66.6%, Pyrazinamide: 79% and Thiocetazone: 57.5%.

**Conclusion:** Most drug-resistant cases of TB were seen among low socioeconomic status people. Ninety-five percent of cases had a history of treatment at least once, hence the resistance was of acquired type. The commonest drug to which bacilli were resistant was Pyrazinamide i.e 73% beside Rifampicin and INH, to which 100% of cases were resistant i.e. MDR TB.

**Key Words:** Tuberculosis, Pulmonary Tuberculosis, Multi-drug resistance

## INTRODUCTION

Tuberculosis (TB) is the most common cause of death due to infectious diseases globally after AIDS <sup>1</sup>. Approximately, 2 billion people in the world are infected with mycobacterium tuberculosis, causing 8.8 million new cases of TB and killing some 2.3 million people very year <sup>2</sup>. The emergence of drug resistant strains of tuberculosis is even a more serious global threat to human health because it is a more severe and difficult to treat infection <sup>3</sup>. According to a World Health Organization (WHO) report, about 50 million persons may be infected with the resistant strains all over the world <sup>4</sup>. In the year 2000, the WHO registered 273000 cases of MDR-TB worldwide <sup>5</sup>. Although no accurate data is available for Pakistan, local studies have reported resistance from 36% to 53% <sup>6, 7</sup>. The existing evidence suggests that it is one of the countries to be worst effected by the drug resistance tuberculosis <sup>8</sup>.

Multi Drug Resistant Tuberculosis (MDR TB), by definition is, a disease caused by strains resistant to at least Rifampicin and Isoniazid <sup>9</sup>. But in practice we come across cases, where an individual may have tuberculosis caused by strains resistant to more or even all the first line anti tuberculous drugs, thereby further complicating the management and outcome of these patients. This study was performed to see the pattern of drug resistance in patients suspected of having MDR TB in our set up.

## MATERIALS AND METHODS

We reviewed the records of those patients, attending chest clinic at Peshawar hospital, who were treated with suspicion of MDR TB between the years 2000-2003. The record of those patients was selected for further analysis, whose sputum smear was positive for Acid Fast Bacilli (AFB) and culture and sensitivity report showed resistance to at least two anti tuberculous drugs i.e Rifampicin & INH. Demographic, Para clinical and radiological data along with treatment were obtained from records.

## RESULTS

The records of 73 patients fulfilled the criteria for further analysis. 43 (56%) were men and 34 (44%) women, with age range of 15-60 years (mean age 32.5 years). Sputum smear was 1+, 2+ and 3+ in 23 (32 %), 23 (32 %) and 27 (36 %) cases respectively. 90% of the patients had a poor socio economic status. The sputum cultures of all patients were positive. Almost all the 73 patients had received anti tuberculosis treatment for at least once. Meanwhile, the history of 2,3, and 4 times of treatment was obtained from 36 (49 %), 20 (28%), and 17 (23%) cases respectively. Culture and sensitivity report showed the following results. 26 patients ( 36 %) were resistant to all six drugs i.e Isoniazid (INH), Rifampicin ( R ), Streptomycin (S), Ethambutal (E), Pyrazinamide (Z) and Thiocetazone (TH). 15 (20%) had resistance to five drugs. 16 patients (22%) were resistant to four drugs while 10 patients (14%) had resistance to three drugs. Only 6 patients (8%) were resistant to combination of Rifampicin and INH i.e 2 drugs. Overall MDR TB turned out to be 100%. Interestingly, the resistance contributed by individual drugs was: Streptomycin: 66.6%, Rifampicin: 100%, INH: 100%, Ethambutal: 66.6%, Pyrazinamide: 79% and Thiocetazone: 57.5%.

## DISCUSSION

MDR TB is defined as disease caused by strains of mycobacterium tuberculosis that are resistant to at least Rifampicin and Isoniazid, the two main anti tuberculous drugs, with or with out resistance to additional drugs <sup>10</sup>. Other less severe forms of drug resistance are mono resistance (resistance to any single agent), or combined resistance, which is resistance to any combination of drugs other than Rifampicin and INH <sup>11</sup>. The resistance may be primary, if the patient has not taken any

anti TB treatment in the past. If it develops in patients who have taken some anti tuberculosis treatment, it is called acquired drug resistance. After clinical assessment, if it is doubtful that the patient really has not received prior treatment, this is called initial resistance. Initial resistance is a mixture of primary resistance and undisclosed acquired resistance <sup>12</sup>.

Acquired MDR-TB arises when TB is improperly managed with incorrect treatment regimens. The most common medical errors leading to the selection of resistant bacilli are, a: the prescription of inadequate chemotherapy to the multi bacillary pulmonary tuberculosis cases (e.g. only 2 or 3 drugs during the initial phase of treatment in a new smear-positive patient with bacilli initially resistant to Isoniazid), b; The addition of one extra drug in the case of failure, and repeating the addition of a further drug in case of no response or when the patient relapses after what amounts to monotherapy <sup>13</sup>. The other factors that contribute to the causation of MDR TB are: a; The difficulty experienced by poor patients in obtaining all the drugs that they need (due to lack of financial resources or social insurance), b; Frequent or prolonged shortages of anti tuberculosis drugs (due to poor management and /or financial constraints in developing countries), c; Use of drugs (or drug combinations) of unproven bioavailability, d; the patient's lack of knowledge (due to a lack of information or due to inadequate explanation before starting treatment) and e; poor case-management (when the treatment is not directly observed, especially during the initial phase).

Prevention of MDR-TB is achieved through the implementation of effective TB control programmes. This implies political commitment in order to guarantee correct operation of the programme, diagnosis based on bacteriological examination, standard short-course chemotherapy provided under directly observed treatment (DOT) at least during the intensive phase of treatment, uninterrupted supply of drugs, and proper recording and reporting of cases and treatment results

<sup>14</sup>

MDR TB and resistance to other multiple combinations of drugs have not only been reported in countries like India, China, parts of Russia and Japan <sup>4,15,16,17</sup> but also in various studies in Pakistan as well <sup>6,7,18,19,20</sup>. As compared to these studies, overall resistance in our study is much higher. 100% of our patients fulfilled the criteria of MDR TB i.e. they were resistant to both Rifampicin and INH at the same time. 26 patients (36 %) were resistant to all six drugs. 15 (20%) had resistance to five drugs. 16 patients (22%) were resistant to four drugs while 10 patients (14%) had resistance to three drugs. Only 6 patients (8%) were resistant to combination of Rifampicin and INH i.e. 2 drugs. The resistance contributed by individual drugs was: Streptomycin: 66.6%, Rifampicin: 100%, INH: 100%, Ethambutal: 66.6%, Pyrazinamide: 79% and Thiocetazone: 57.5%. Haq MU<sup>6</sup> at King Edward Medical College Lahore found MDR TB in 11% of the isolates. 36% of the bacterial isolates were resistant to one or more drugs. 14% isolates had resistance to one drug, 13% to two drugs, 5% to three drugs and 4% to all the four drugs. While overall resistance to individual drugs was streptomycin 19%, rifampicin 15%, isoniazid 25%, and ethambutol 12%. In a study by Iqbal R and colleagues <sup>7</sup> at PMRC TB research center Lahore, MDR TB was reported in 26 % of his patients and pattern of resistance to individual drugs was: streptomycin 24%, rifampicin 28%, isoniazid 26%, ethambutol 15%, pyrazinamide 29%. In another study by Butt T <sup>18</sup> at Department of Microbiology, Armed Forces Institute of Pathology, Rawalpindi, in which 1359 Pulmonary and extra pulmonary specimen from suspected cases of TB were studied and mycobacterium tuberculosis was isolated from 325 clinical specimens, the overall resistance to individual drug was streptomycin 19%, rifampicin 32%, isoniazid 37%, ethambutol 17% and MDR TB in 32% patients. Studies by Almani SA<sup>19</sup> and Rasul S <sup>20</sup> also showed similar pattern of drug resistance. The resistance pattern in all

these studies were almost consistent to each other but overall resistance in this study was very high as we studied drug resistance pattern particularly in patients where it was highly suspected by history of intake of multiple irregular drug courses in past and lack of clinical response. Majority of the study patients had acquired drug resistance. Ninety-five percent of them had a history of at least single course of treatment, confirming that acquired drug resistance is the most prevalent form of resistance in our population.

### **Conclusion:**

Most drug-resistant cases of TB were seen among low socioeconomic status people. Ninety-five percent of cases had a history of treatment at least once, hence the resistance was of acquired type. The commonest drug to which bacilli were resistant was Pyrazinamide i.e 73% beside Rifampicin and INH, to which 100% of cases were resistant i.e. MDR TB. The expansion of DOTS is the standard strategy recommended for efficient control of TB and prevents the emergence MDRTB.

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